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Solid support linker strategies
[Review article]
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Abstract:
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Solid support linker strategies

Bradley J Backes* and Jonathan A Ellman†

The selection of an appropriate linker is critical to the success of any strategy for the solid-phase synthesis of small molecule libraries. While the primary function of the linker is to covalently attach the initial substrate to the support, innovative strategies have emerged recently in which linkers fulfill important auxiliary roles. These include the cleavage of compounds into solution leaving no trace of the support attachment site, cleavage via cyclization, cleavage by introduction of additional diversity into the structure, and cleavage whereby portions of the compound are sequentially released into solution.

Addresses
Department of Chemistry, University of California at Berkeley, Berkeley CA 94702, USA
*e-mail: backes@uclink4.berkeley.edu
†e-mail: jellman@uclink.berkeley.edu

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Abbreviations

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DMF	*N,N*-dimethyl formamide
HF	hydrofluoric acid
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyranyl ether

Introduction

Combinatorial technologies encompass numerous strategies to prepare and screen collections or 'libraries' of structurally related molecules [1,2]. Although library approaches have had an impact on the fields of materials development, catalysis, and molecular recognition [3•], the major application has been the development of new therapeutic agents. The focus of these efforts has shifted to small molecule libraries [4•,5•] from peptide and oligonucleotide libraries since these biopolymers typically suffer from poor oral availability and rapid *in vivo* clearance.

General and high yielding synthesis methods must be devised in order to prepare structurally and functionally diverse small molecule libraries. While several solution-phase methods have been developed [4•,5•], to date the majority of library synthesis efforts have employed the solid-phase strategies pioneered by Merrifield for peptide synthesis [6]. The methods for substrate attachment to the support and the final cleavage of the products into solution are crucial features of all solid-phase strategies. The primary function of the linker is simply to covalently attach the substrate to the support. However, innovative linkage strategies have emerged that allow for the cleavage of compounds into solution leaving no trace of the support attachment site, cleavage via cyclization, and cleavage by introduction of additional diversity into the structure. Linkers can also fulfill auxiliary roles in the synthesis of optically pure compounds and in the deconvolution of assay mixtures.

The following review will provide an overview of new linkage strategies for small molecule synthesis and combinatorial library applications from 1992 to the present, focusing primarily on the advances of the past two years. Many carboxylic acid- and amide-based linkers utilized for solid-phase peptide synthesis [7] have been adapted to small molecule synthesis. These developments have been reviewed elsewhere [4•,5•] and will not be discussed.

General considerations for library synthesis

In solid-phase synthesis strategies, a substrate is attached to a functionalized polymer. Reactive polymers are prepared using copolymerization processes that incorporate functionalized monomers, or by direct derivatization of the polymer itself [8]. A functionalized polymer is typically coupled to a linker compound or 'handle' that provides the desired site for attachment of the substrate [9•]. 'Preformed handle' strategies are those in which the handle is attached to the substrate in solution, and subsequently coupled to the polymer. Preformed handle strategies are effective when attaching a template or scaffold upon which diversity is introduced. Direct loading of the substrate onto the resin-bound linker is necessary when attaching multiple substrate building blocks.

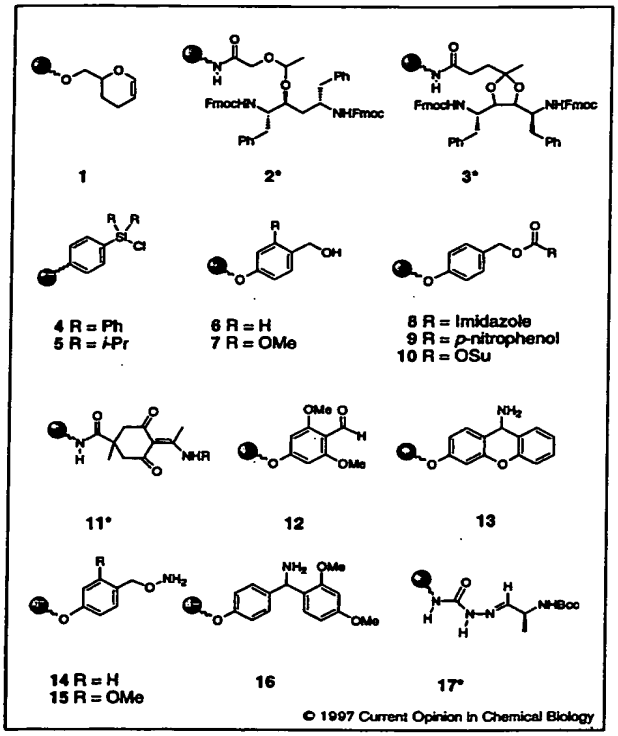
For the solid-phase synthesis of small molecules, the choice of a linkage strategy deserves special consideration because linker stability and cleavage conditions dictate the range of synthetic chemistries that can be employed. A successful linkage strategy has the same requirements as a solution-phase protecting group strategy: quantitative loading (protection), chemical stability during the synthesis sequence (orthogonality), and quantitative cleavage (deprotection) without product degradation. Synthesis in a library format has the additional requirement that the cleavage conditions employed should not complicate rapid compound isolation.

Protecting-group linker strategies

For most library synthesis efforts the initial building block or scaffold bears functionality (carboxylic acid, phenol, alcohol, amine etc.) that is covalently attached to a support-bound protecting group. After the structure is elaborated, the target compound is cleaved, bearing the same functionality. The development of new protecting-group linkers is certain to provide researchers with more

flexibility when planning a synthesis strategy. Only a brief summary of new advances will be given since these strategies are conceptually similar to their solution-phase counterparts.

Figure 1



Protecting-group linkers. Linkers used to attach compounds to the support through functionality present in the initial substrate and the final library products. A preformed handle approach has been employed with linkers marked with an *.

Figure 1 shows linkers used in protecting-group linker strategies. All bold numbers refer to the structures shown in the figures. In early solid-phase synthesis reports, ester [10] and trityl ether [11,12] functionalities served to tether alcohols to a support. More recently, tetrahydropyranyl ether- (THP) **1** [13], acetal- **2** [14,15], ketal- **3** [16], silyl ether- **4**, **5** [16,17] as well as carbonate-based linkages [18] have been utilized. For phenol attachment, Wang resin **6** is routinely employed to provide a *p*-alkoxybenzyl ether linkage [19]. Acid-labile benzyl carbamate based linkers for tethering amines to support were originally developed for amino→carboxyl peptide synthesis [20,21]. Functionalized resins **8** [22], **9** [23], and **10** [24] have recently been employed to provide a more labile *p*-alkoxybenzyl carbamate linkage. A palladium-labile allyl carbamate-based linkage has also been described [25]. The ADCC 1* amine protecting group inspired the preparation of resin **11** [26]; the linkage is stable to trifluoroacetic acid (TFA) and stable to the bases piperidine and DBU, but is readily cleaved by 2% hydrazine in DMF. The THP linker **1** described above has also been used for attaching 2,6-dichloropurine to a support through the N-9 nitrogen [27]. Resin **12** [28] and the commercially available Seiber resin **13** [29] have been reductively aminated employing amines and aldehydes, respectively, to give support-bound amines. Additionally, trityl chloride resins are commonly employed for anchoring amines, diamines and amino alcohols to supports [30].

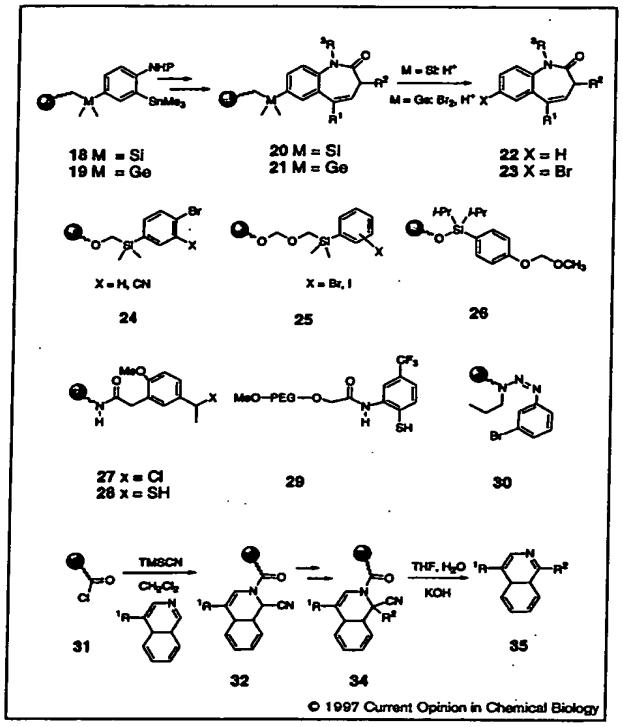
Linkage through pharmacophore-based functional groups is particularly useful because this site of a molecule is not varied in a library synthesis [31]. Alkoxyamine resins **14** [32,33] and **15** [32] allow for the synthesis of the hydroxamic acid functionality, a pharmacophore for metalloprotease inhibition. Rink **16** [34], Wang **6** [35], and Sasrin **7** [35] resins have all been utilized to provide sulfonamide-based linkages, and a semicarbazone-based linker (**17**) has been developed for anchoring amino acid aldehydes to support [36]. In addition, a phosphonate ester-based linkage has been employed for the synthesis of α-amino [37] and α-hydroxy phosphonates [38].

Traceless linker strategies

Protecting-group linkage strategies are most useful when the unmasked functionality is important for the biological activity of the target compounds. Since auxiliary polar functionality can adversely affect the pharmacokinetic properties or binding properties of the target compounds, 'traceless' linker strategies have been devised that leave the target compound with no 'memory' of solid-phase synthesis (Fig. 2). Several metal-based aryl linkers have been described that permit cleavage with electrophilic reagents, often introducing additional diversity. In an early report, benzodiazepines were prepared using an aminoaryl stannane attached to the support through a silyl linkage **18** [39*]. Treatment with HF provides benzodiazepines (shown as **22**) free of auxiliary functionality. A more labile germanium derivative (**19**) has been prepared for the same purpose [40]. Arylsilane-based linkers **24** [41] and **25** [42*] and a silyl ether based linker **26** [43] have been reported as well. Electrophilic cleavage employing Br_2 [40,42*] and ICl [42*] to provide bromine and iodine substituted aromatic products has been demonstrated in addition to protodesilation by acidolysis [40,41,42*] or basic fluoridolysis [41,43]. All of the reported metal-based aryl linkers utilize preformed handle strategies. It is likely that new strategies will be developed that provide more efficient loading of the substrate onto the solid support.

Traceless strategies that do not incorporate metals include thioether- **27** [44], **28** [45], **29** [45] and triazine- **30** [46] based linkers. For all of the strategies described in this section, the linkage group is replaced by either a hydrogen or halogen substituent, thus leaving a subtle

Figure 2



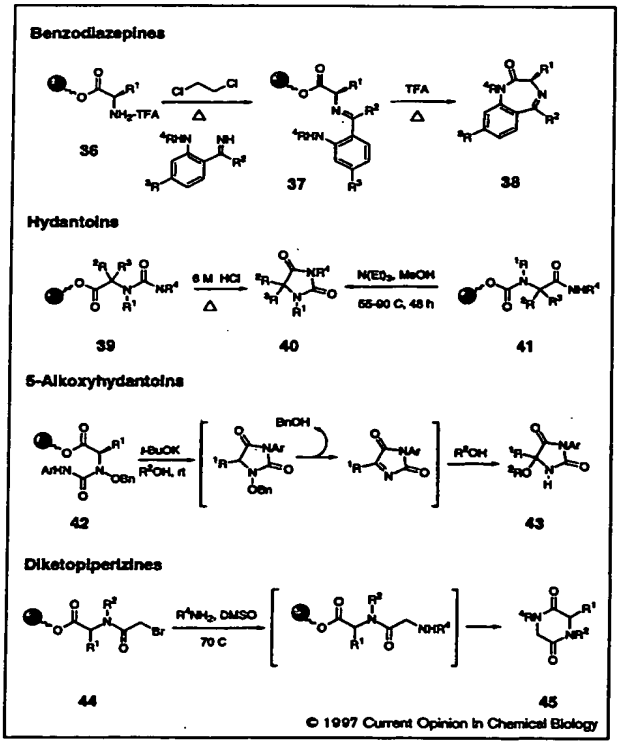
Traceless linkers. Linkers used to cleave compounds into solution leaving no trace of the support attachment site.

mark of attachment. A true traceless linkage strategy has been developed for the synthesis of isoquinolines [47•]. Hydrolysis of Reissert complex 34 results in elimination of cyanide to provide isoquinoline products devoid of any evidence of solid-phase synthesis.

Release by cyclization strategies

The release of compounds into solution by cyclization, whereby a reactive functionality closes down upon the support attachment site, provides a useful cleavage method. Linkers used in these strategies are shown in Figure 3. Typically, an unmasked support-bound nucleophile closes down upon a carbamate- or ester-based linkage, releasing the target compound into solution. Naturally, these strategies are limited to compounds that possess rings. It should be noted that due to competing intersite reactions [48], release by cyclization of rings larger than 5–6 members can result in substrate dimerization and resin cross-linking [49]. While these strategies can provide products in high purity when support-bound deletion sequences do not cleave into solution, a high fidelity synthetic sequence is still required to obtain uniform yields. Amino acids linked through a C-terminal ester linkage (36) have been employed for the synthesis of benzodiazepines 38 and hydantoins 40 with acid-promoted cleavage [50]. Hydantoins have also been prepared using a base-promoted cyclization method employing a carbamate linkage 41 [51]. A recently reported strategy to provide 5-alkoxyhydantoins (43) permits the introduction of additional elements of diversity to the library after release into solution during the cleavage step [52]. Diketopiperazines (45) have been prepared [53,54] using a strategy that results in *in situ* release when R^1 substituents are not sterically demanding [53]. In addition, base-promoted cyclization strategies have been employed to prepare 3-substituted quinazoline-2,4-diones [55], 5,6-dihydropyrimidine-2,4-diones [56], and 1,4-benzodiazepine-2,5-diones [57]. Cyclizations have also been performed in solution after cleavage of the compounds from the support. High fidelity syntheses are especially important for solution cyclization strategies since deletion sequences or side products are also released into solution. Diketopiperazines [58], diketomorpholines [53], and β-turn mimetics [59] have been prepared in this manner.

Figure 3



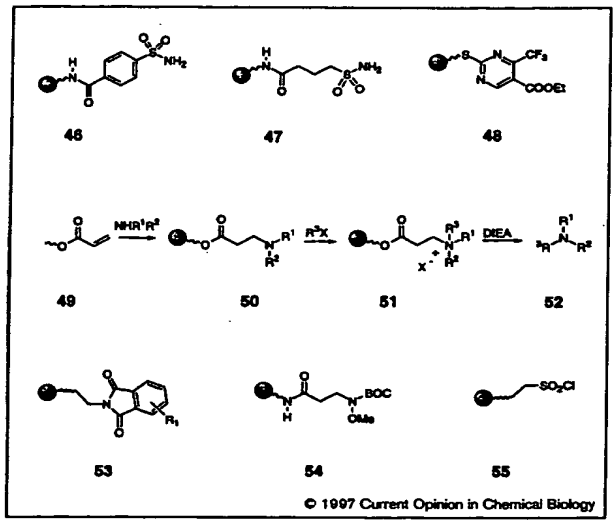
Linkers used in release by cyclization. Synthesis strategies in which target compounds are released via cyclization.

Diversification linker strategies

Linkage strategies in which diverse substituents are incorporated into the target compound upon cleavage

are particularly useful for combinatorial synthesis efforts. Figure 4 details examples of these linkers. When synthesizing a library, it is desirable to employ limiting quantities of the cleavage agent, which results in products in solution that do not require further purification. The use of polymer-supported covalent scavengers [60•] and sequestering agents [59,61] may provide access to pure products even when excess cleavage reagents are used. In an early report, a method was described to transesterify benzyl ester-based linkages with various alcohols under relatively mild conditions (LiBr and DBU in THF)[62]. Benzyl ester-based linkages have also been cleaved by aminolysis to give a range of amide products using aluminum trichloride [63] and trimethyl aluminum [64] reagents to promote the reaction. The harsh conditions employed and reagent byproducts produced may limit the generality of these methods. More reactive esters prepared from commercially available Kaiser's oxime resin [65,66] can be cleaved under mild conditions with amine nucleophiles to provide amide products in solution [67].

Figure 4



Diversification linkers. Linkers used to incorporate diverse substituents into the target compounds in the cleavage steps.

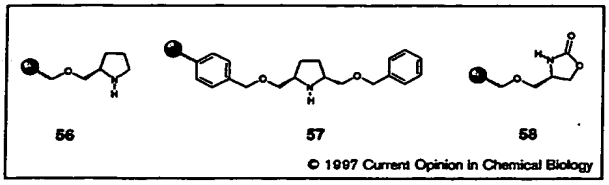
High reactivity towards cleavage limits the range of chemistry that can be employed during library synthesis. To address this problem, 'safety-catch' linkers that provide a more chemically stable linkage have been developed. A chemoselective activation step after solid-phase synthesis is complete provides a reactive linkage element for cleavage. Kenner's arylsulfonamide safety-catch linker, **46**, provides a carboxylic acid linkage stable to both acid and base [68,69]. Activation via *N*-alkylation with diazomethane and cleavage with hydrazine, amine and alkoxy nucleophiles gives hydrazide, amine, ester, and acid products in solution. Recently, a haloacetonitrile activation method has been reported that provides a highly reactive linkage for cleavage [70•]. Limiting amounts of nucleophilic amines can be added to the support-bound *N*-cyanomethyl acylsulfonamide, resulting in complete conversion to provide pure amide products in solution. In order to apply this activation method to benzoic acid and carboxylic acids that possess α-electron withdrawing groups such as amino acids, a second alkyl sulfonamide linker (**47**) was prepared. A sulfur-based safety-catch linker (**48**) prepared by direct loading of a thiol resin has been employed for the synthesis of small heterocycles [71•]. After an oxidative activation step, nucleophilic cleavage with limiting amounts of various amines provides substituted heterocycles. A safety-catch linker for the synthesis of 3° amines has also been described [72•]. Michael addition of an amine to acrylate ester resin (REM linker) **49** provides a support-bound 3° amine (**50**) for further elaboration. Quaternization with a variety of reactive alkylating reagents introduces diversity, and at the same time provides a labile linkage. Hoffman elimination with Hunig's base gives relatively pure 3° amines and regenerates the REM linker.

Additional diversification linkage strategies that do not involve an activation step have also been reported. Phthalamide resin **53** has been employed for the synthesis of phthalhydrazides [73]. Cleavage of **53** with substituted hydrazides provide the corresponding phthalhydrazide products. In preliminary studies, the addition of Grignard reagents to Weinreb amide linker **54** was employed to provide ketone products [74]. A related Weinreb amide linker was previously reported for the synthesis of α-*N*-acylamino aldehydes [75]. Treatment of alkyl sulfonyl chloride resin **55** [76] with alcohols provides mesylate-based linkages to the support. Mesylate displacement with NaI has been demonstrated to afford alkyl iodide products. The authors of [75] suggest that the mesyl linkage could be used for a wide range of substitution reactions.

Support-bound chiral auxiliaries

Polymer-supported chiral auxiliaries [77] for carrying out diastereoselective transformations to provide enantiomer-enriched compounds upon cleavage have been reported (representative examples are shown in Fig. 5). Since chirality is an important determinant in receptor recognition, this class of linkers could be particularly useful for the preparation of lead optimization libraries. Kurth and co-workers utilized polymer-bound auxiliary **56** [78] and C_2-symmetric auxiliary **57** [79] for preparing optically active 3,5-disubstituted-γ-butyrolactones. In addition, a reusable polymer-bound 'Evans' oxazolidinone (**58**) has been reported [80]. Diastereoselective enolate alkylation was demonstrated with hydrolytic cleavage to provide enantiomerically-enriched α-alkylated carboxylic acids [80].

Figure 5

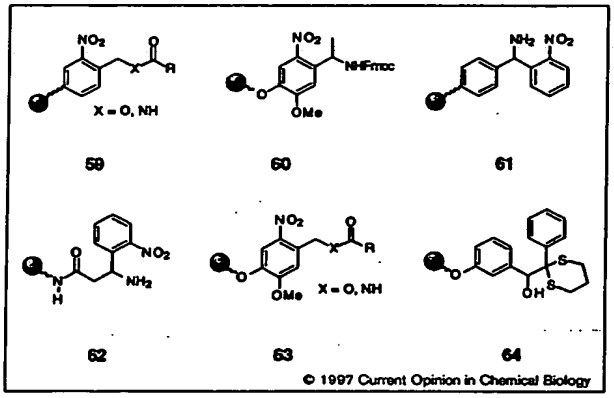


Support-bound chiral auxiliaries.

Photolabile linkers

Photolabile linkers [7] deserve special consideration since photolysis can provide an orthogonal and noninvasive cleavage strategy allowing for the direct assay of the cleaved library. Figure 6 shows examples of photolabile linkers. Photolabile linkers based upon the nitrobenzyl group, represented by 59, have been used extensively to provide ester- and amide-based linkages to the support. Related photolabile anchors have been employed for tethering alcohols [18,81–83] and amines [84] to support, mainly through carbonate and carbamate linkages, respectively. Photolysis liberates the target compound, resulting in the formation of a support-bound nitroso aldehyde. This functionality can trap liberated compounds, for example by reaction with 1° amines to give support-bound imines. Accordingly, photolabile linkers 60 [85], 61 [86], 62 [87], which provide a less reactive nitroso ketone functionality upon photolysis, have been developed. The nitroso byproducts can dimerize to form azo compounds that act as an internal light filter which retards the rate of cleavage. Methoxy substituents have been introduced to nitrobenzyl linkers to provide nitroveratryl-based linkers (63), since nitroveratryl groups have much higher absorbtivity at the excitation wavelength than do nitrobenzyl groups. It should be noted, however, that Krafft *et al.* [88] have determined that the quantum yield for photodeprotection of nitroveratryl groups can be much lower than for nitrobenzyl groups, resulting in comparable cleavage photoefficiencies. One major limitation of photolabile linkers is chemical instability. The nitro functionality is unstable to most reducing agents and many organometallic reagents. In fact, the issue of chemical instability has inspired the recent development of a safety-catch photolabile linker (64) [89] that is activated towards photolytic cleavage by thioketal deprotection.

Figure 6

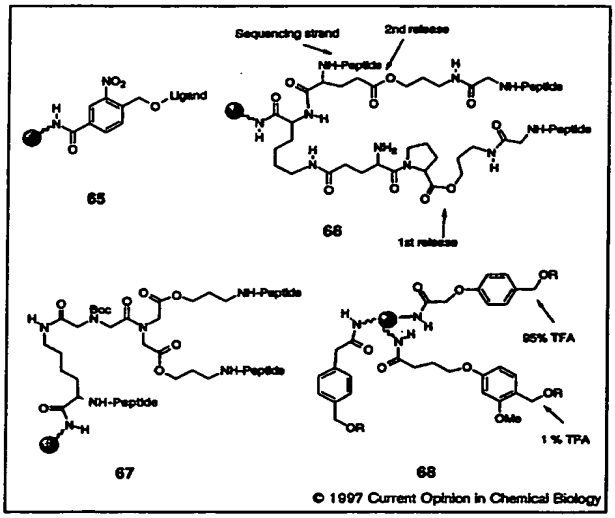


Photolabile linkers. Linkers that permit photolytic cleavage.

Linkers for deconvolution

For some deconvolution approaches, that is to say the evaluation of progressively smaller pools of compounds to identify the active compound, partial release of the support-bound compound into solution is required. Photolabile linkers are ideal for the controlled partial release of compounds into solution (Fig. 7). As demonstrated for photolabile linker 65, long-wavelength UV light facilitates partial release, allowing multiple determinations to be made from a single bead in conjunction with solution assays [82].

Figure 7



Linkers for deconvolution. Linkers used for the partial cleavage of compounds into solution for deconvolution strategies.

A second strategy for partial compound release is to employ multiple linkers that are cleaved under different reaction conditions. Multiple release linker 66 [90], which has been used for deconvolution studies to identify active peptides, relies on orthogonal cleavage conditions. One third of the peptide strands are cleaved at neutral pH via diketopiperazine formation, and one third are released at high pH via saponification. The identity of

the remaining support-bound peptide strand is determined by microsequencing. A related doubly-cleavable linker for peptide synthesis (**67**) has also been reported [91]. A portion of the support-bound compound is cleaved via diketopiperazine formation after protecting group removal with TFA. A second portion can then be cleaved under basic conditions. Multiple linkers have also been used in which compound release is governed by the relative acid lability of the linkers **68** [92]. It should be noted that multiple linker strategies drastically limit the range of chemistry that can be performed in a synthesis sequence since all synthesis steps must be orthogonal to the different cleavage strategies employed. The general utility of multiple release linkers for the synthesis of small molecule libraries is therefore likely to be limited.

Conclusions

The methods for compound attachment to the support and cleavage into solution are crucial features of all solid-phase strategies. While the primary function of a linker is to covalently attach the initial substrate to a support, general approaches have been developed in which linkers fulfill important auxiliary roles. In this review we have described general strategies for four cleavage types: the cleavage of compounds into solution leaving no trace of the support attachment site; cleavage via cyclization; cleavage by introduction of additional diversity into the structure; and cleavage whereby portions of the compound are sequentially released into solution. An increasing number of researchers are applying library strategies to a host of research problems in chemistry and biology. The development of new linkage strategies will be driven by the need to prepare libraries of new compound classes as required to address specific research problems. A majority of these new linkage strategies will fall within one of the designated linker categories.

Acknowledgements

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